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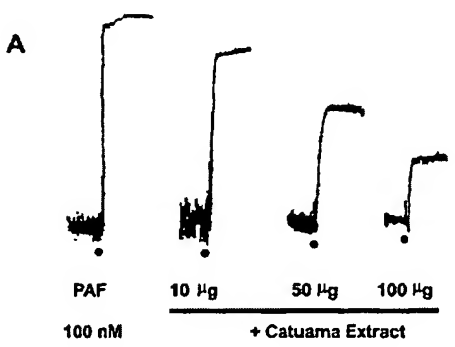
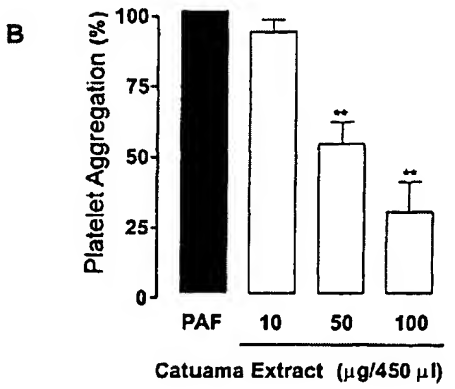
(54) Title: USE OF A PRODUCT COMPRISING CATUAMA EXTRACT AS AN ANTITHROMBOEMBOLIC AGENT





(57) Abstract: This invention relates to the use of a product comprising Catuama extract, comprising the species *Trichilia sp.* (preferably of the species *catigua*), *Paullinia cupana* (*Sapindaceae*), *Ptychopetalum olacoides* (*Olacaceae*) and *Zingiber officinale* (*Zingiberaceae*), wherein said product is an antithromboembolic agent. A product particularly encompassed by the scope of the invention is Catuama extract commercially available as Catuama[R].

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Title: **"USE OF A PRODUCT COMPRISING CATUAMA EXTRACT AS AN ANTITHROMBOEMBOLIC AGENT, PHARMACEUTICAL COMPOSITION COMPRISING SUCH PRODUCT FOR TREATING OR PREVENTING THROMBOEMBOLIC DISORDERS, METHOD FOR TREATING THROMBOEMBOLIC DISORDERS USING SAID PRODUCT AND USE OF SAID PRODUCT FOR MANUFACTURING A PHARMACEUTICAL COMPOSITION FOR TREATING OR PREVENTING THROMBOEMBOLIC DISORDERS".**

Field of the Invention

The present invention relates to the use of a product comprising Catuama extract, comprising species of *Trichilia sp.*, particularly *Trichilia catigua* (*Meliaceae*), *Paullinia cupana* (*Sapindaceae*), *Ptychopetalum olacoides* (*Olacaceae*) and *Zingiber officinale* (*Zingiberaceae*).

Background of the Invention

Medicinal plants known as catuaba (Trichilia sp.) have recognized uses, due to their aphrodisiac activities, as a tonic and in the treatment of physical and mental fatigue.

Already known are, e.g., phytotherapeutic formulations prepared from extracts of catuaba plants, which can be used alone or in combination with other medicinal plant extracts, such as guarana. A number of alternative formulations containing extracts of other species of catuaba are already well-known from the state-of-the-art, all of them being related to the tonic and stimulating effect of this group of plants.

There also exists in the art phytotherapeutic products comprising a combination of extracts of plants from the *Trichilia sp.* species, particularly *Trichilia catigua* (*Meliaceae*), *Paullinia cupana* (*Sapindaceae*), *Ptychopetalum olacoides* (*Olacaceae*) and *Zingiber officinale* (*Zingiberaceae*).

A commercially available product comprising extracts of the above-mentioned plants in combination with suitable carriers is Catuama®. More particularly, the product Catuama® is a phytotherapeutic widely used in Brazil. Its composition consists of 4 extracts from medicinal plants including: catuaba (Trichilia catigua, A. juss, Meliaceae - (husk)), guarana

(Paullinia cupana, K., Sapinadaceae - (seed)), muirapuama (Ptychopetalum olacoides, B., Olacaceae - (root)) and ginger (Zingiber officinale, L., Zingiberaceae - (rhizome).

Summary of the Invention

The present invention refers to the use of a product of the extract of Catuama comprising *Trichilia sp.*, particularly *Trichilia catigua* (*Meliaceae*), *Paullinia cupana* (*Sapindaceae*), *Ptychopetalum olacoides* (*Olacaceae*) and *Zingiber officinale* (*Zingiberaceae*), as an antithromboembolic agent.

In another aspect, this invention refers to pharmaceutical compositions comprising said extracts having antithromboembolic activities.

In yet another aspect, this invention refers to a method for treating and/or preventing thromboembolic disorders using said extract of Catuama.

In still another embodiment, the invention refers to the use of a product comprising extract of *Trichilia sp.*, particularly *Trichilia catigua* (*Meliaceae*), *Paullinia cupana* (*Sapindaceae*), *Ptychopetalum olacoides* (*Olacaceae*) and *Zingiber officinale* (*Zingiberaceae*), for preparing a pharmaceutical composition for the treatment and/or prevention of thromboembolic disorders.

Detailed Description of the Invention

After extensive studies, the inventors have found that the extract of Catuama, comprising *Trichilia sp.*, particularly *Trichilia catigua* (*Meliaceae*), *Paullinia cupana* (*Sapindaceae*), *Ptychopetalum olacoides* (*Olacaceae*) and *Zingiber officinale* (*Zingiberaceae*), has extraordinary antithromboembolic activities.

As used herein "antithromboembolic activities" includes activities related to disorders such as: unstable angina or acute myocardial infarction; ischemic coronary syndromes in patients having undergone coronary angioplasty or arteriectomy; ischemic heart complications related to the abrupt obstruction of the treated coronary artery; thromboembolic disorders of any etiology or localization, including those from surgical procedures and delivery complications and thromboangiitis obliterans, Raynaud's disease, diabetes,

acrocyanosis etc., such as: intermittent claudication; trophic disorders, pregangrene, varicose ulcers, paresthesia, nocturnal cramps, cold extremities; disorders associated to consumption coagulopathy, thrombosis coagulopathy in patients suffering from nephrotic syndrome, as well as digestive diseases coagulopathy, and also those with inadequate or no response to heparin; in pre-eclampsia; thromboembolic diseases (specially in general and orthopedic surgery), peripheral vasculopathies and cerebrovascular alterations, prevention of postsurgical venous thrombosis, of myocardial reinfarction, of atherosclerotic injuries, and vascular diseases in patients with platelet hyperactivity; postthromboembolic disorders treated with streptoquinase such as, e.g., in disseminated intravascular coagulation, myocardial infarction, inhibition of coagulation upon using extracorporeal circulation (surgeries) or hemodialysis; already existing deep venous thrombosis, prophylaxis of deep venous thrombosis and recurrences, prophylaxis of pulmonary thromboembolism; prophylaxis and therapeutics of hyperlipidemia; treatment and/or prophylaxis of atherosclerotic events in patients with atherosclerosis caused by recent stroke or acute myocardial infarction (AMI); existing peripheral arterial disease; treatment and/or prophylaxis of pulmonary embolia, acute and subacute peripheral arterial thrombosis and chronic occlusive arterial disease, retinal artery or central vein occlusion; treatment and/or prevention in phlebology: varices and varicosities; venous failure (edema, weight sensation in the legs, etc.), consequences of thrombophlebitis, pre-ulcerous conditions and varicose ulcers, and posttraumatic edemas.

A number of products comprising varying concentrations of extract of the above plants are commercially available. The use thereof, so far recommended in the art, is related to the treatment of physical and mental fatigues, neuromuscular asthenia and weariness.

Studies and research now carried out by the present inventors show new antithromboembolic activities related to products based on the above mentioned extracts as confirmed by the data and tests disclosed herein.

The concentration of the extract of each plant of *Trichilia sp.*,

particularly *Trichilia catigua*, *Paullinia cupana*, *Ptychopetalum olacoides* and *Zingiber officinale*, in the product or pharmaceutical composition of the present invention ("Product comprising extract of Catuama") is as follows:

Liquid formulation:		
Component	% (m/v)	
	Generic	**Preferred**
Extract of *Trichilia sp* (specially *Trichilia catigua)*	0.50 to 5.50	0.50 to 5.0
Extract of *Paullinia cupana*	0.10 to 7.50	0.1 to 5.0
Extract of *Ptychopetalum olacoides*	0.01 to 5.50	0.01 to 5.0
Extract of *Zingiber officinale*	0.10 to 2.00	0.1 to 0.40
Suitable excipient	79.50 to 99.29	84.60 to 99.24

Solid formulation:		
Component	% (m/m)	
	Generic	**Preferred**
Extract of *Trichilia sp* (specially *Trichilia catigua)*	5 to 50	30 to 50
Extract of *Paullinia cupana*	2 to 30	10 to 21
Extract of *Ptychopetalum olacoides*	0.2 to 15.0	5.0 to 12
Extract of *Zingiber officinale*	0.50 to 3.0	0.5 to 1.50
Suitable excipient	2.0 to 92.30	15.5 to 54.5

In its dry and excipient-free form, extract of Catuama comprises:

Formulation		
Component	% (m/m)	
	Generic	**Preferred**
Extract of *Trichilia sp* (specially *Trichilia catigua)*	17 to 40.0	22.0 to 34.0
Extract of *Paullinia cupana*	24.0 to 57.0	32.0 to 48.0
Extract of *Ptychopetalum olacoides*	17.0 to 40.0	22.0 to 34.0
Extract of *Zingiber officinale*	2.0 to 5.0	2.5 to 4.0

The product may comprise usual excipients for formulation such

as preservatives, colorants, carriers, etc. Adequate excipients are well known by those skilled in the art and do not constitute limiting aspects of the invention.

For the purposes of the present invention, all plants of the genus *Trichilia* were found to be useful, such as, e.g., *T. catigua A. Juss.*, *T. clausseni C. DC.*, *T. casaretti C. DC.*, *T. pallida Swartz.* and *T. elegans A. Juss.* According to a preferred embodiment of the present invention, it was found that, among the genera comprised of species *Trichilia sp.*, *Trichilia catigua* is particularly suitable for the intended purposes. Additionally, the materials extracted from *Trichilia sp.* are preferably fragments of the whole plant, more preferably stalk, which are advantageously used as extract, more preferably they are formulated with pharmaceutically acceptable inert carriers. Formulations of Trichilia sp. useful for the present invention can be administered, e.g., orally in the form of tablets, coated tablets, hard and soft gelatin capsules, solutions, emulsions and suspensions; or rectally, in the form of suppositories. Suitable carriers include, but are not limited to, lactose, starch or derivatives thereof, talc, stearic acid or salts thereof in the case of solid formulations for oral administration. Suitable carriers for soft gelatin capsules include vegetable oils, waxes, fats, semi-solid and liquid polyols. Solutions may be prepared comprising selected carriers such as water, polyols and carbohydrates. In the case of suppositories, suitable carriers comprise natural or hardened oils, waxes, fats and polyols.

In addition to the carriers, the formulations of the Catuama extract according to the present invention may contain preservative agents, solubilizing agents, stabilizers, wetting agents, emulsifiers, sweeteners, coloring agents, flavoring agents, tonicity adjustment substances, buffers, coating agents or antioxidants.

However, an effective dosage for administration to humans was found to be in the range from 10 mg to 0.5 g of Catuama extract.

In the case of pharmaceutical formulations containing Catuama extract, the intended effects can be effectively obtained using from 0.2 to 50% by weight of said extract, based on the total formulation.

The invention will now be described specifically referring to the applicant's product having the name Catuama®, that is already commercialized in Brazil for the treatment of several chronic diseases such as physical and mental fatigue, neuromuscular asthenia and weariness. The pharmaceutical formulations available allow the product to be administered orally. Another advantage of the product is associated with the lack of any reported undesirable or side effects, even when the product is used for long periods of time.

Together, the results discussed herein show that the Catuama extract referred to in this invention (specially Catauma®) exhibits antithromboembolic effects, specially when used regularly and for extended periods of time.

The present invention relates to the Catauma extract effects on pathologies involving vascular alterations essentially in combating and/or preventing thromboembolic disorders. Cardiovascular dysfunctions, specially those related to atherosclerosis and vascular integrity of small arteries are, without doubt, relevant and are frequently associated with the occurrence of high mortality rates. Several substances released by endothelial cells, including NO (nitric oxide) and prostacyclins, inter alia, are responsible for vascular smooth muscle relaxation and inhibition of platelet aggregation. More and more such substances have their activity associated with diverse pathologies. The decrease in the NO content is usually associated with a reduction in the activity of the enzyme NO synthase, changes in calcium influx and the increase of apoptosis of endothelial cells. The deficiency in endothelium-dependent vascular contractility may also cause important alterations in the contractile response by various neurotransmitters and local factors, thus worsening the vascular "rigidity" state. A change in the vascular endothelium may cause hyperplasia and an increase in platelet adhesion, which in turn, releases potent growing factors. Vascular and extravascular endothelial intervention can thus be useful for the treatment and prevention of cardiovascular and/or atherosclerotic pathologies in young and old patients.

Thus, the inhibiting effect on platelet aggregation observed for the Catuama extract is of importance, principally in cases where there is a need for chronic administration. The product does not cause alterations in blood coagulation, thus having reduced side effects.

Brief Description of the Drawings

Figure 1 shows the plasma platelet aggregation profile in healthy human volunteers (A). Platelet aggregation was induced by the addition of PAF (100 nM) in the presence or absence of Catuama extract. The effect of Catuama extract (10-100 μg/sample) on the plasma PAF (100 nM)-induced platelet aggregation of healthy human volunteers (B) is also shown. Each group represents the average of 6 volunteers and the vertical bars represent the E.P.M. It significantly differs from the control group, **P < 0.01.

Figure 2 shows the plasma platelet aggregation profile in healthy human volunteers (A). Platelet aggregation was induced by the addition of ADP (10 μM) in the presence or absence of Catuama extract. The effect of Catuama extract (10-100 μg/sample) on the plasma ADP (10 μM)-induced platelet aggregation of healthy human volunteers (B) is also shown. Each group represents the average of 6 volunteers and the vertical bars represent the E.P.M. It significantly differs from the control group, **P < 0.01.

Figure 3 shows the effect of Catuama extract (10-400 μg/ sample) on ADP (20 μM)-induced platelet aggregation in plasma from guinea-pig blood. Each group represents the average of 6 animals and the vertical bars represent the E.P.M. It significantly differs from the control group, **P < 0.01.

Figure 4 shows the effect of the chronic treatment (seven days) in rats with Catuama extract (20 mg/kg) orally or a carrier on ADP (1-10 μM)-induced platelet aggregation in rat blood. Each group represents the average of 4 to 5 animals and the vertical bars represent the E.P.M.

Figure 5 shows the effect of the sub-chronic treatment (seven days) in rats with Catuama extract (200 mg/kg) or a carrier on the inhibition of ADP (10-20 μM)-induced platelet aggregation caused by acetylsalicylic acid in rat blood. Each group represents the average of 4 to 5 animals and

the vertical bars represent the E.P.M.

Figure 6 shows the effect of Catuama extract (40-80 μg/ml) on *in vitro* clotting time by the prothrombin method. The results are expressed as the average ± E.P.M. The asterisks indicate the significance when compared to the control group, *$p < 0.05$ ($n = 6$).

Figure 7 shows the effect of Catuama extract (40-80 μg/ml) on *in vitro* clotting time by the activated partial thromboplastin method. The results are expressed as the average ± E.P.M. The asterisks indicate the significance when compared to the control group, *$p < 0.05$ ($n = 6$).

The illustrative test examples below are given for a better description of the present invention. However, the data and procedures illustrated therein refer to certain embodiments of the present invention and are not to be construed as limiting the scope thereof.

The following tests were carried out using a composition of extracts in the solid and dry form (herein referred to as Catuama extract) as follows:

Formulation	
Component	% (m/m)
Extract of *Trichilia sp* (specially *Trichilia catigua)*	29.5
Extract of *Paullinia cupana*	37.6
Extract of *Ptychopetalum olacoides*	29.5
Extract of *Zingiber officinale*	3.4

A - Effect on platelet aggregation factor (ADP)- or adenosine diphosphate-induced platelet aggregation (PAF) in platelet-rich plasma from rabbit, rat and human blood.

Platelet-rich plasma (PRP) was obtained by centrifuging whole blood at 1500 rpm for 10 minutes at room temperature. After separation of PRP, the remaining blood was subjected to a new centrifugation at 3500 rpm for 10 minutes in order to obtain the respective platelet-poor plasma (PPP). Immediately after obtaining the PRP, it was transferred, by means of an automatic pipette, into plastic tubes, which were sealed with parafilm and used within a period of, at most, 3 hours after the collection of the material.

Platelet counting was carried out with an 1% ammonium oxalate solution using an optical microscope.

The aggregometer consists of a photometer kept at 37°C and equipped with a device which maintains the sample under continued stirring and to which a recorder can be coupled allowing the accompaniment of light transmission variation , while platelet response occurs (Zucker, 1989). Born and Cross's turbidimetric method (1983) is based on the principle of transmittance increase through a platelet solution when aggregation is induced.

The aggregation tests were carried out in a final volume of 470 µl, as follows: aliquots of PRP (450 µl) were transferred into silicone glass cuvettes, to which 10 µl of the platelet aggregation-inducing drugs or compounds to be tested were added.

PAF (100 nM)- or ADP (10 µM)-induced platelet aggregation was verified in blood of healthy male human volunteers in the presence or absence of Catuama extract (10-100 µg/sample) or a carrier.

PAF (10 nM)- and ADP (20 µM)-induced platelet aggregation were verified in blood of male and female guinea-pigs in the presence or absence of Catuama extract (10-400 µg/sample) or a carrier.

The results from the platelet aggregation assays are shown below:

The incubation of PRP with Catuama extract at varying concentrations (10-100 µg/sample) resulted in concentration-dependent inhibition on PAF (100 nM)-induced platelet aggregation (figure 1) or ADP (100 µM)-induced platelet aggregation (figure 2) in human blood. Maximum Inhibitions and 50% Inhibitory Concentrations (CI_{50}s) are shown in Table 1.

In plasma from guinea pigs, incubation of PRP with Catuama extract (10-1000 µg/sample) inhibited ADP (20 µM)-induced platelet aggregation (figure 3). The CI_{50} and Maximum Inhibition of Catuama extract are shown in Table 1.

Table 1 - 50% Inhibitory Concentrations (CI_{50}) and Maximum Inhibitions (I_{max}) obtained for the Catuama extract in PAF (10-100 nM)- or ADP (10-20 µM)-platelet aggregation in human and guinea pig plasma.

Extract	Aggregating agent	Species	CI_{50} (µg/sample)	$I_{máx}$ (%)
Catuama extract	PAF	Human	52.46 (37.14- 74.10)	70.11 ± 10.52
	ADP	Human	70.75 (37.47-133.57)	58.73 ± 6.45
	ADP	Guinea-pig	49.37 (40.97-59.50)	88.91±1.22

The 50% Inhibitory Concentrations (CI_{50}) are given under µg/sample and Maximum Inhibitions (I_{max}) are given under % maximum effect. Each group represents the average of 6 animals.

In another experimental group, groups of rats were treated orally (v.°), once a day, for seven days, with Catuama extract (200 mg/kg), acetylsalicylic acid (100 mg/kg) or with a carrier only (control group) . On the seventh day, 6 hours after the last treatment, blood was collected from these animals and the PRP was subjected to ADP (0,5-20 µM)-induced platelet aggregation.

A possible interference of the treatment on the inhibition of platelet aggregation caused by acetylsalicylic acid (50-800 µg/sample) was also checked in the plasma of the groups treated subchronically (seven days) with the Catuama extract (200 mg/kg).

The results from the platelet aggregation assays, after subchronic treatment, are shown hereinbelow.

Subchronic treatment (seven days) in rats with Catuama extracts (200 mg/kg) orally did not significantly change ADP (0.5-20 µM)-induced platelet aggregation (figure 4). The CE_{50}s for ADP (0.5-20 µM) in the control group or the group treated with Catuama extract were: 2.50 (0.86-7.24) and 2.66 (1.28-5.54) µM, respectively. The CE_{50}s for ADP were calculated from the concentration-response curve with five points (distinct for each group) of concentrations of ADP.

The inhibition of platelet aggregation caused by acetylsalicylic acid (50-800 µg/sample) was not significantly changed when the rats were subchronically (seven days) treated with Catuama extract (200 mg/kg) (figure 5).

B - Measurement of the prothrombin time (PT) and the activated partial thromboplastin time (PTT_A)

Reconstituted Simplastin® Excel S, heated at 37°C, was the reactant used for determining PT and the *in vitro* assay was carried out according to the methodology described (Pelzer et al., 1968; Tanabe et al., 1999). Samples of plasma (0.1 ml) containing Catuama extract (40-80 μg/ml), heparin or water from milli-Q (control group) were placed into plastic test tubes (disposable, 8 ml) and kept in a water bath at 37°C for 3 to 10 minutes. Then 0.2 ml of "Simplastim® Excel S" (previously heated) was rapidly added to the tubes containing the different plasmas and, at the same time, the quantification of the time required to form the clot was initiated. The clotting time for the different samples was measured in seconds and carried out in duplicate.

To determine PTT_A, reactant Platelin® LS was used and an *in vitro* assay was carried out according to the methodology previously described (Tanabe et al., 1999). Samples of plasma (0.1 ml) containing Catuama extract (40-80 μg/ml), heparin or water from milli-Q (control group) were placed into plastic test tubes (disposable, 8 ml), 0.1 ml of reactant was added and then they were kept in a water bath at 37°C for 5 minutes. Following this, 0.1 ml of the calcium chloride solution (25 mM) was added and, at the same time, the quantification of the time required to form the clot was initiated. The clotting time for the different samples was measured in seconds, with the experiments being carried out in duplicate.

The results obtained from the assays of measurement of the prothrombin time (PT) and the activated partial thromboplastin time (PTT_A) are shown hereinbelow.

Incubation of Catuama extract (at concentrations varying from 40 to 80 μg/ml) was not able to cause any changes in the clotting time, both when analyzed by the prothrombin method (figure 6) and the activated partial thromboplastin (figure 7). On the other hand, incubation of heparin (100 μg/ml) used as the reference drug caused a significant increase in the clotting time by the two methods used.

CLAIMS

1. Use of a product comprising Catuama extract, comprising the species *Trichilia sp.*, *Paullinia cupana* (*Sapindaceae*), *Ptychopetalum olacoides* (*Olacaceae*) and *Zingiber officinale* (*Zingiberaceae*), wherein said product is an antithromboembolic agent.

2. The use of claim 1, wherein the composition of said product is as follows

Liquid formulation:		
Component	% (m/v)	
	Generic	**Preferred**
Extract of *Trichilia sp* (specially *Trichilia catigua)*	0.50 to 5.50	0.50 to 5.0
Extract of *Paullinia cupana*	0.10 to 7.50	0.1 to 5.0
Extract of *Ptychopetalum olacoides*	0.01 to 5.50	0.01 to 5.0
Extract of *Zingiber officinale*	0.10 to 2.00	0.1 to 0.40
Suitable excipient	79.50 to 99.29	84.60 to 99.24

Solid formulation:		
Component	% (m/m)	
	Generic	**Preferred**
Extract of *Trichilia sp* (specially *Trichilia catigua)*	5 to 50	30 to 50
Extract of *Paullinia cupana*	2 to 30	10 to 21
Extract of *Ptychopetalum olacoides*	0.2 to 15.0	5.0 to 12
Extract of *Zingiber officinale*	0.50 to 3.0	0.5 to 1.50
Suitable excipient	2.0 to 92.30	15.5 to 54.5

or in its dry and excipient-free form, comprises:

Formulation		
Component	% (m/m)	
	Generic	**Preferred**
Extract of *Trichilia sp* (specially *Trichilia catigua)*	17 to 40.0	22.0 to 34.0
Extract of *Paullinia cupana*	24.0 to 57.0	32.0 to 48.0
Extract of *Ptychopetalum olacoides*	17.0 to 40.0	22.0 to 34.0
Extract of *Zingiber officinale*	2.0 to 5.0	2.5 to 4.0

3. The use of any of the preceding claims, wherein said product is Catuama®.

4. The use of any of the preceding claims, for the treatment and/or prevention of unstable angina or acute myocardial infarction, or ischemic coronary syndromes in patients having undergone coronary angioplasty or arteriectomy.

5. The use of any of the preceding claims, for avoiding ischemic heart complications related to the abrupt obstruction of the treated coronary artery.

6. The use of any of the preceding claims, for the treatment of thromboembolic disorders of any etiology or localization, including those from surgical procedures and delivery complications; disorders associated to consumption coagulopathy, thrombosis coagulopathy in patients suffering from nephrotic syndrome, as well as digestive diseases coagulopathy, and also those with inadequate or no response to heparin; or in pre-eclampsia.

7. The use of any of the preceding claims, for the treatment of thromboembolic diseases (specially in general and orthopedic surgery), peripheral vasculopathies and cerebrovascular alterations, prevention of postsurgical venous thrombosis, prevention of myocardial reinfarction, of atherosclerotic injuries, and vascular diseases in patients with platelet hyperactivity

8. The use of any of the preceding claims, for postthromboembolitic treatment with streptoquinase such as, e.g., in the disseminated intravascular coagulation, myocardial infarction, inhibition of coagulation upon using extracorporeal circulation (surgeries) or hemodialysis

9. The use of any of the preceding claims, for the treatment and/or prophylaxis of hyperlipidemias.

10. The use of any of the preceding claims, for the treatment and/or prophylaxis of atherosclerotic events in patients with atherosclerosis caused by recent stroke or acute myocardial infarction (AMI) or existing peripheral arterial disease.

11. The use of any of the preceding claims, for the treatment

and/or prophylaxis of pulmonary embolia, acute and subacute peripheral arterial thrombosis and chronic occlusive arterial disease, retinal artery or central vein occlusion.

12. The use of any of the preceding claims, for the treatment and/or prevention of pulmonary thromboembolia.

13. The use of any of the preceding claims, for the treatment and/or prevention in phlebology: varices and varicosities; venous failure (edema, weight sensation in the legs etc.), thromboangiitis obliterans, Raynaud's disease, diabetes, acrocyanosis, trophic disorders, pre-gangrene, paresthesia, nocturnal cramps, cold extremities; consequences of thrombophlebitis, pre-ulcerous conditions and varicose ulcers, and posttraumatic edemas.

14. A pharmaceutical composition comprising Catuama extract, comprising the species *Trichilia catigua* (*Meliaceae*), *Paullinia cupana* (*Sapindaceae*), *Ptychopetalum olacoides* (*Olacaceae*) and *Zingiber officinale* (*Zingiberaceae*) for the treatment and/or prevention of any thromboembolic disorders.

15. The pharmaceutical composition of claim 14, wherein said product has a composition as defined in claim 2.

16. The pharmaceutical composition of any of claims 13, 14 or 15, wherein said product is Catuama®.

17. The pharmaceutical composition of any of the preceding claims, wherein said pharmaceutical composition is used for the treatment and/or prevention of any of the disorders as described in claims 2 to 14.

18. A method for treating and/preventing thromboembolic disorders, comprising administering a product of Catuama extract comprising the species *Trichilia sp.* (*Meliaceae*), *Paullinia cupana* (*Sapindaceae*), *Ptychopetalum olacoides* (*Olacaceae*) and *Zingiber officinale* (*Zingiberaceae*) to a patient in need thereof.

19. The method of treatment and/prevention of claim 18, wherein said product has a composition as defined in claim 2.

20. The method of treatment and/prevention of any of the pre-

ceding claims, wherein said product is Catuama®.

21. The method of treatment and/prevention of any of the preceding claims, wherein said method is used for the treatment and/or prevention of any disorders as described in claims 2 to 14.

22. Use of a product comprising Catuama extract, comprising the species *Trichilia sp.* (*Meliaceae*), *Paullinia cupana* (*Sapindaceae*), *Ptychopetalum olacoides* (*Olacaceae*) and *Zingiber officinale* (*Zingiberaceae*), wherein said product is used for preparing a pharmaceutical composition for the treatment and/or prevention of thromboembolic disorders.

23. The use of claim 22, wherein said product has the composition as defined in claim 2.

24. The use of any of claims 22 or 23, wherein said product is Catuama®.

25. The use of any of claims 22, 23 or 24, wherein said product is used for the treatment and/or prevention of any of the disorders as described in claims 2 to 14.

Fig. 1

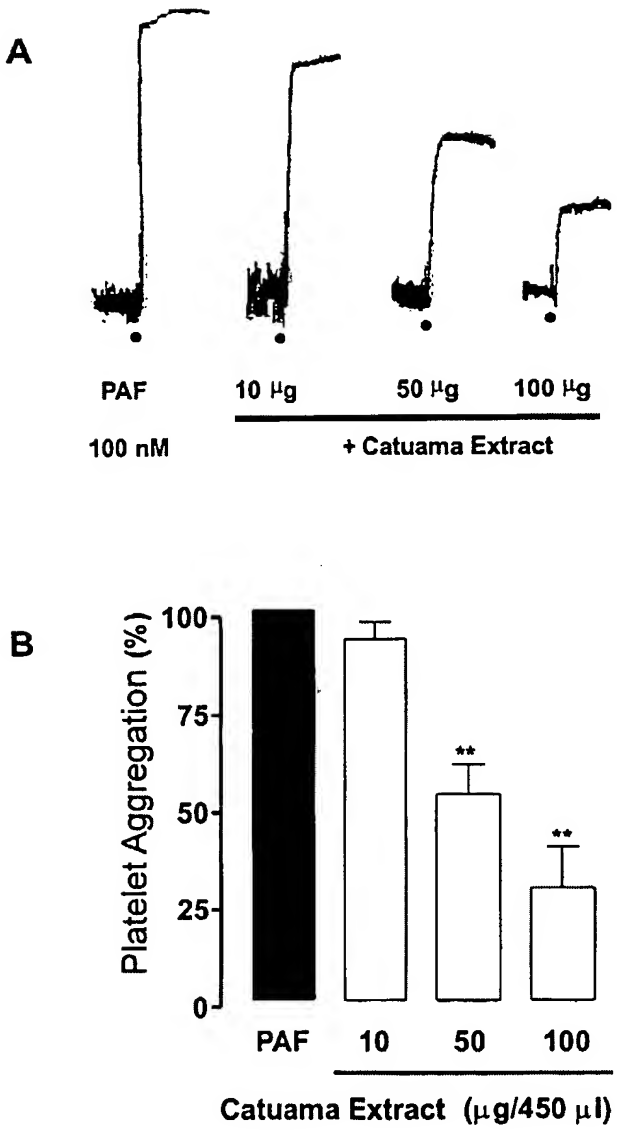

A
PAF
100 nM
10 µg
50 µg
100 µg
+ Catuama Extract
B
Platelet Aggregation (%)
100
75
50
25
0
**
**
PAF
10
50
100
Catuama Extract (µg/450 µl)

Fig. 2

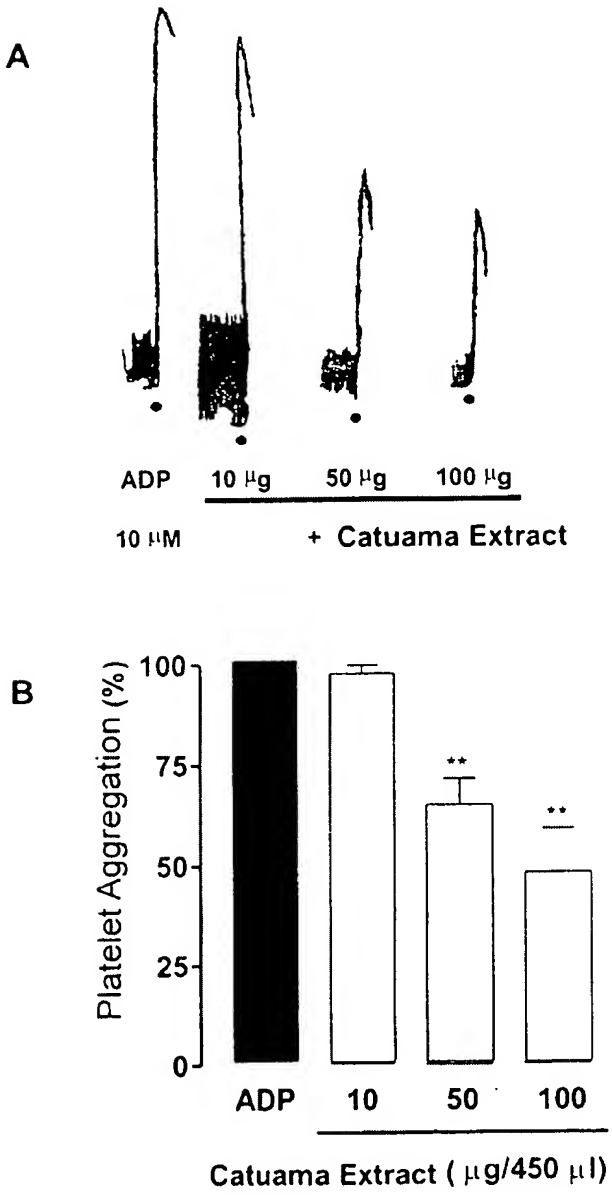

A
ADP
10 µg
50 µg
100 µg
10 µM
+ Catuama Extract
B
Platelet Aggregation (%)
100
75
50
25
0
**
**
ADP
10
50
100
Catuama Extract (µg/450 µl)

Fig. 3

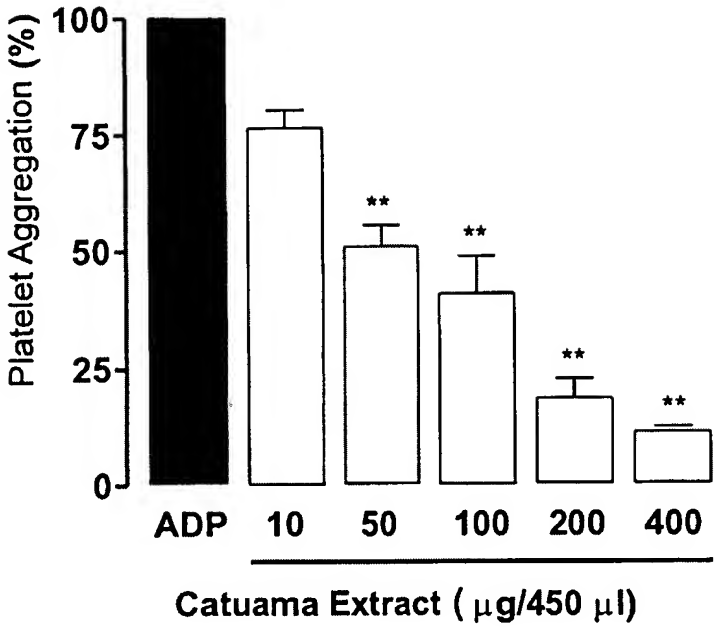

Platelet Aggregation (%)
100
75
50
25
0
**
**
**
**
ADP
10
50
100
200
400
Catuama Extract (µg/450 µl)

Fig. 4

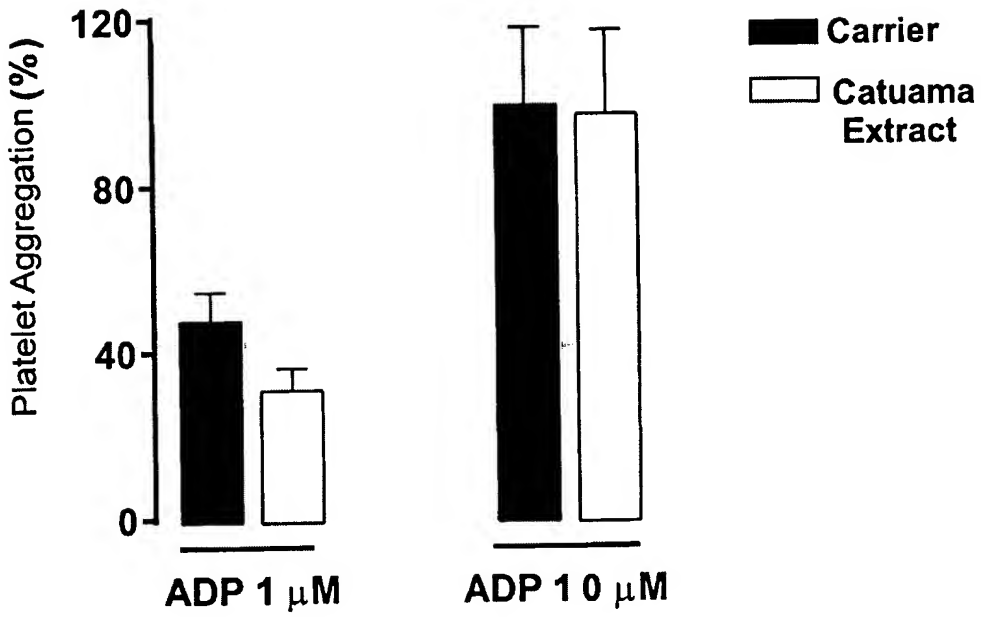

Platelet Aggregation (%)
120
80
40
0
ADP 1 μM
ADP 10 μM
Carrier
Catuama Extract

Fig. 5

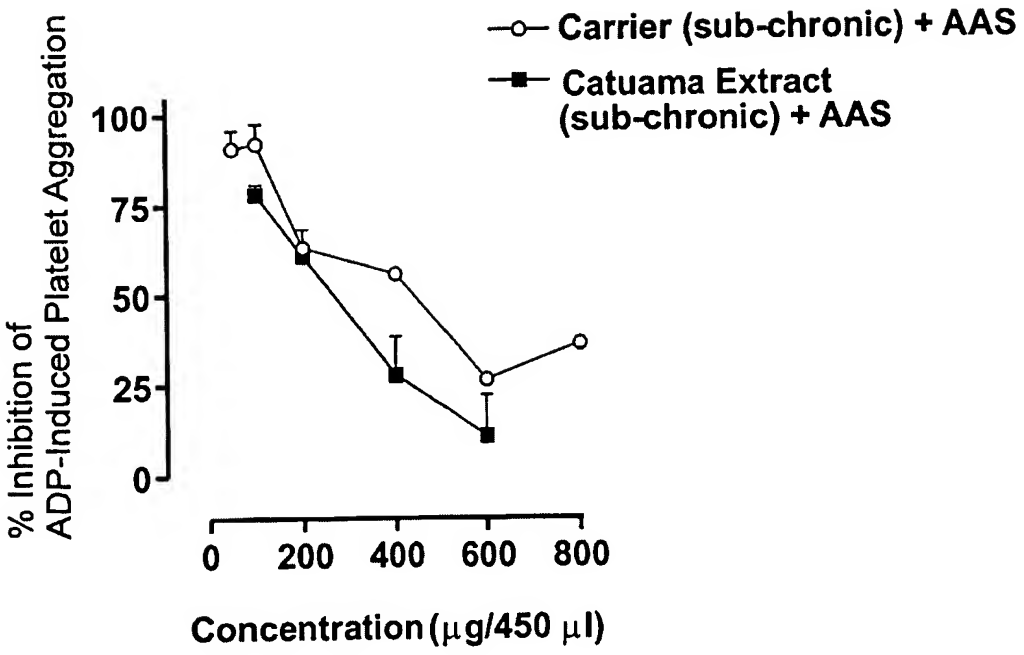

Carrier (sub-chronic) + AAS
Catuama Extract (sub-chronic) + AAS
% Inhibition of ADP-Induced Platelet Aggregation
100
75
50
25
0
0
200
400
600
800
Concentration (µg/450 µl)

Fig. 6

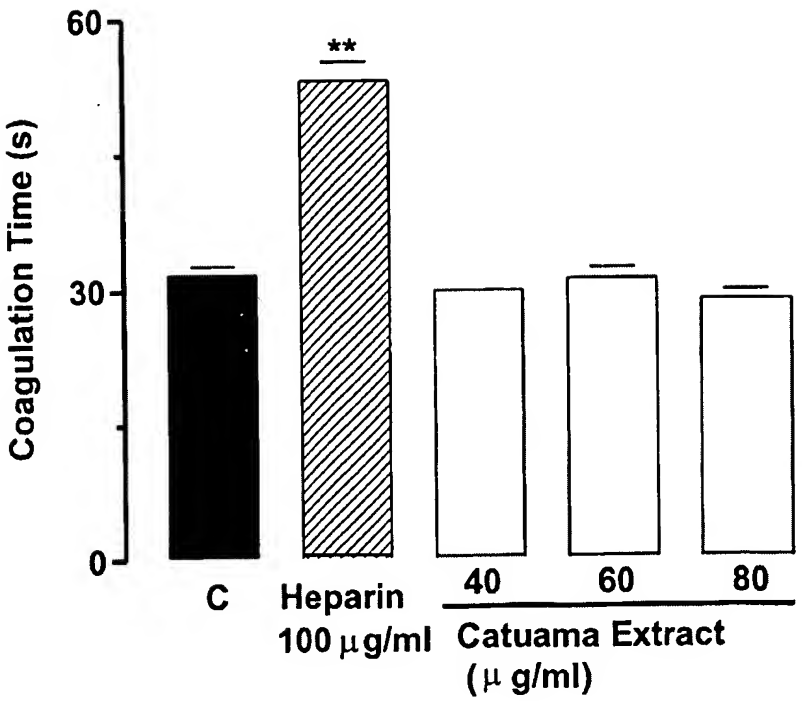
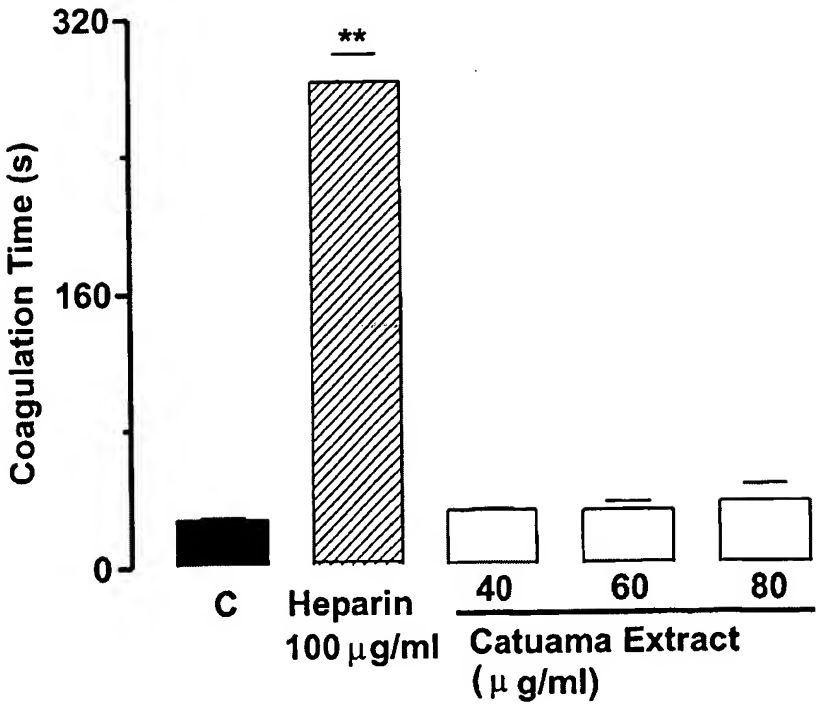

60
30
0
Coagulation Time (s)
**
C
Heparin
100 µg/ml
40
60
80
Catuama Extract
(µ g/ml)

Fig. 7


320
160
0
Coagulation Time (s)
**
C
Heparin
100 µg/ml
40
60
80
Catuama Extract
(µ g/ml)

INTERNATIONAL SEARCH REPORT

Ir onal Application No
PCT/BR 01/00093

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61P7/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, FSTA, MEDLINE, PASCAL, LIFESCIENCES, CHEM ABS Data, CAB Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CALIXTO J B ET AL: "HERBAL MEDICINE CATUAMA INDUCES ENDOTHELIUM-DEPENDENT AND -INDEPENDENT VASORELAXANT ACTION ON ISOLATED VESSELS FROM RATS, GUINEA-PIGS AND RABBITS" PHYTOTHERAPY RESEARCH, JOHN WILEY & SONS LTD. CHICHESTER, GB, vol. 11, no. 1, 1 February 1997 (1997-02-01), pages 32-38, XP002061880 ISSN: 0951-418X the whole document --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 May 2002	13/05/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rempp, G

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BR 01/00093

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	VAZ Z R ET AL: "ANALGESIC EFFECT OF THE HERBAL MEDICINE CATUAMA IN THERMAL AND CHEMICAL MODELS OF NOCICEPTION IN MICE" PHYTOTHERAPY RESEARCH, JOHN WILEY & SONS LTD. CHICHESTER, GB, vol. 11, no. 2, 1 March 1997 (1997-03-01), pages 101-106, XP002061879 ISSN: 0951-418X	
A	WO 99 02172 A (CATARINENSE S A LAB ;MIKIO KASSUYA ROBERTO (BR); MOREIRA EDUARDO A) 21 January 1999 (1999-01-21)	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 4-13,18-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 4-13,18-21

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/BR 01/00093

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9902172 A	21-01-1999	BR 9703946 A	09-03-1999
		AU 3843697 A	08-02-1999
		WO 9902172 A1	21-01-1999
		JP 2001509486 T	24-07-2001
		US 6335039 B1	01-01-2002